Case Study

National Biofilms Innovation Centre

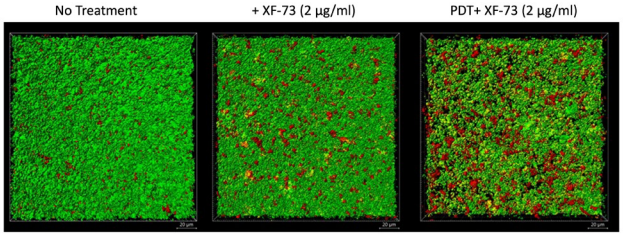
BREAKING BIOFILM AMR

Helping to support biofilm models to assess novel interventions

Biofilms are a major cause of antimicrobial resistance (AMR) and are recognised as a key factor in the inability of antibiotics (and other antibacterial agents) to treat many types of chronic, recurring infections e.g., diabetic foot ulcers and cystic fibrosis-associated pneumonia. Bacterial biofilms are communities of bacteria embedded within a self-secreted, mainly polysaccharide, slime matrix. This matrix acts as a protective mechanism against a range of external threats, including antibiotics. The development of new agents which can overcome biofilm-associated AMR thus represents a considerable unmet clinical need.

Previous studies have shown the efficacy of a novel XF-drug activity against Methicillin Resistant *Staphylococcus aureus* (MRSA) biofilms in laboratory *in-vitro* models. With the support of NBIC Proof of Concept funding, a project led by Destiny Pharma sought to expand the knowledge of XF-drug activity against clinically relevant biofilms, including those formed by other high priority, multidrug resistant (MDR) bacterial species on the World Health Organisation priority pathogen list, including *Pseudomonas aeruginosa*. Since XF-drugs have two distinct mechanisms of anti-microbial action, innate and photodynamic, both of these modes of activity were explored in this study. NBIC also supported the project by providing expertise in the skin explant wound model, biofilm growth and experiments and imaging methodologies, as well as access to clinically relevant microorganisms from *ex-vivo* clinical samples.

The compound was highly effective at killing biofilms formed by clinical *Staphylococcus aureus* strains in the pig skin explant model, achieving complete kill (no remaining viable bacterial cells). Photodynamic



Killing of Staphylococcus aureus by XF-73, with and without PDT treatment. Bacteria labelled with Live/Dead stain (live bacteria fluoresce green and dead bacteria fluoresce red). Confocal laser scanning microscopy, scale bar = 20 µm.

therapy (PDT) greatly enhanced the activity against *Staphylococcus aureus.* The compound also showed some efficacy against *Pseudomonas aeruginosa* strains, achieving 90% reduction in viability. 3-dimensional Confocal laser scanning microscopic (CLSM) imaging was also carried out to evaluate the killing of *Staphylococcus aureus* in biofilms. The project evolved as planned, although optimisation of the wound model was required to avoid complete overgrowth of *Pseudomonas aeruginosa* and *Staphylococcus aureus* in the model during infection. The work supported an existing platform of Destiny Pharma IP including three families of patents with a total of 95 granted patents and two pending patents. Destiny Pharma's Chief Strategy Officer Dr Bill Love said,

"NBIC have been entirely supportive of the research programme, particularly in regard to the impact of Covid 19, allowing for timeline extensions which take this impact into consideration".

The project is now complete, however future studies could explore efficacy against complex multi-species communities of bacteria, for example containing *Pseudomonas aeruginosa* and *Staphylococcus aureus* and potentially other pathogens in co-culture as might be more representative of a wound infection.

Dr Bill Love

Dr Love is a former scientist at Novartis, focused on novel drug delivery technologies. Dr Love founded Destiny Pharma and leads the development of XF-73 and NTCD-M3. He is an expert advisory board member of the UK government's Global AMR Innovation Fund as well as its COVID-19 Research and Innovation Taskforce. He has experience in drug R&D from discovery through to Phase 1/2/3 clinical development in the UK, EU and US.